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EXAMINER	
GRASER, JENNIFER E	

ART UNIT	PAPER NUMBER
1645	14

DATE MAILED: 10/29/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 10/049,473	Applicant(s) DE GROOT ET AL.	
	Examiner Jennifer E. Graser	Art Unit 1645	

-- The MAILING DATE of this communication appears on th cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *20-38* is/are pending in the application.

4a) Of the above claim(s) *28,29,34 and 35* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *20-27,30-33 and 36-38* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *13* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Election/Restriction-Telephone Election

1. Restriction is required under 35 U.S.C. 121 and 372.

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1.

In accordance with 37 CFR 1.499, applicant is required, in response to this action, to elect a single invention to which the claims must be restricted.

Group I, claim(s) 20-27, 30-33 and 36-38, drawn to proteins, vaccine comprising said proteins, method of making said proteins and methods of immunizing using said proteins.

Group II, claim(s) 28 and 29, drawn to antibodies and method of obtaining said antibodies.

Group III, claim(s) 34 and 35, drawn to nucleic acid.

The inventions listed as Groups I-III do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: the Groups each contain a special technical feature which is biologically, structurally and chemically different from the other Groups.

During a telephone conversation with Edna Gergel on September 17, 2003 a provisional election was made without traverse to prosecute the invention of Group I, claims 20-27, 30-33 and 36-38. Affirmation of this election must be made by applicant in replying to this Office

action. Claims 28, 29, 34 and 35 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a petition under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(I).

Claim Objections

2. The numbering of claims is not in accordance with 37 CFR 1.126 which requires the original numbering of the claims to be preserved throughout the prosecution. When claims are canceled, the remaining claims must not be renumbered. When new claims are presented, they must be numbered consecutively beginning with the number next following the highest numbered claims previously presented (whether entered or not).

Misnumbered claims 19-37 have been renumbered as claims 20-38.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 20-27, 30-33 and 36-38 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 20 and 27 are vague and indefinite because it is unclear what structures are encompassed by the terms "fragment thereof", "homologous" and or a "functionally homologous protein or protein fragment thereof". The terms "fragment" and "homologous" read on as little as one amino acid. The specification provides no clear definition or description of the structure of a fragment which would still function as a "protease maturation" peptide. Additionally, the function of the claimed protein has been based solely on sequence homology analysis and not actual testing of the protein. Accordingly, the metes and bounds of the claim cannot be understood. Clarification is requested.

Claim 20 is vague and indefinite because it recites using a *S.pneumoniae* protein to treat *any* microbial infection (see last line of the claim). The claim encompasses treatment of infections caused by such diverse bacteria as *M.tuberculosis, P.aeruginosa, C.botulinum, N.meningitidis,* etc.. Clearly, this is not the intent of the vaccine/preparation. Clarification is requested.

Claims 20-27, 30-33 and 36-38 are vague and indefinite due to the term "medical preparation". It is unclear what this phrase encompasses. Is this equivalent to a 'pharmaceutical composition' or an 'immunogenic composition'? If so, one of the latter terms is preferable. Correction is requested.

Claim 24 is vague and indefinite because it is unclear what is encompassed by the term "anchoring fragment". What is the immunogen anchored to? Additionally, the terms "antigenic fragment or a functional equivalent thereof" and "functional equivalent of a receptor binding site or an antibody binding site" are also vague and indefinite. What antibodies or receptors is the claim referring to and what is considered a functional equivalent of these sites?

Claims 25 is vague and indefinite due to the phrase "wherein said protein or said fragment comprises a purified, recombinant or synthetic protein or fragment thereof". It is unclear what is meant by "a protein which comprises a protein'. Do the claims mean to state "wherein said protein [of claim 20] is a synthetic or recombinant protein"? The current claim does not convey this. Additionally, the current claims reads on 'fragments of fragments'. As stated in the rejection of claim 20 above, the terms "fragment" reads on as little as one amino acid. The specification provides no clear definition or description of the structure of a fragment which would still function as a "protease maturation" peptide. Clarification is requested.

Claim 26 is vague and indefinite because it recites a fragment which 'comprises at least 8 amino acids' yet it is unclear which 8 amino acids if any fragments out of the 322 amino acids of the full-length protein are responsible for the protease maturation function. Clarification is requested.

Claims 19, 20, 27, 31, 36, 37 and 38 should refer to the sequence by sequence identifier alone, i.e., SEQ ID NO:2.

Claims 30, 31, 37 and 38 provides for the use of a protein, but, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

Claims 30, 31, 37 and 38 are rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd.* v. *Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

Claim 36 is vague and indefinite because it is unclear what structures are encompassed by the terms "fragment thereof", "homologous" and or a "functionally homologous protein or protein fragment thereof". The terms "fragment" and "homologous" read on as little as one amino acid. The specification provides no clear definition or description of the structure of a fragment which would still function as a "protease maturation" peptide. Additionally, only the nucleic acid sequence set forth in SEQ ID NO:1 which encodes the full-length protein has been disclosed. It is unclear what the gene encoding equivalent or homologous sequences would look like. The claim is also vague and indefinite due to the term "obtainable" because a positive recitation of the function is required. If Applicants wish to claim a recombinant protein, it is suggested that the claim be amended to recite "A recombinant protease maturation protein comprising the amino acid sequence as shown in SEQ ID NO:2." Clarification is requested.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 20-27, 30-33 and 36-38 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The instant claims are drawn to vaccines or medical preparations comprising a protease maturation protein of *S.pneumoniae* comprising an amino acid sequence as shown in SEQ ID NO:2 and/or a fragment thereof and/or a homologous and/or a functionally homologous protein or protein fragment thereof for the treatment of microbial infections. Fragments as small as 8 amino acids are claimed. Methods for vaccination and treatment using vaccines or medical preparations comprising a protease maturation protein of *S.pneumoniae* comprising an amino acid sequence as shown in SEQ ID NO:2 and/or a fragment thereof and/or a homologous and/or a functionally homologous protein or protein fragment thereof are also included in the scope of the invention.

Enablement requires that the specification teach those in the art to make and use the invention without undue experimentation. Factors to be considered in determining whether a disclosure would require undue experimentation include (1) the nature of the invention, (2) the

state of the prior art, (3) the predictability or lack thereof in the art, (4) the amount of direction or guidance present, (5) the presence or absence of working examples, (6) the quantity of experimentation necessary, (7) the relative skill of those in the art, and (8) the breadth of the claims.

The breadth of the instant claims contain proteins and amino acid sequences other than what is specified in the sequence disclosure. The specification states that substitutions, additions, or deletions may be made to the defined sequences; however, the specification provides no guidance as to what amino acids may be changed without causing a detrimental effect to the protein to be produced. Further, it is unpredictable as to which amino acids could be removed and which could be added. While it is known that many amino acid substitutions are possible in any given protein, the position within the protein's sequence where amino acid substitutions can be made with a reasonable expectation of success are limited. Other positions are critical to the protein's structure/function relationship, e.g., such as various positions or regions directly involved in binding, catalysis in providing the correct three-dimensional spacial orientation of binding and catalytic sites. These regions can tolerate only very little or no substitutions. The instant claims are drawn to proteins which are homologous or vary from a given protein; i.e., equivalent sequences, homologous sequences, fragments, etc.. The position and individual amino acid residues in peptide antigen-antibody interactions is extremely important. Selective point mutation to one key antigen residue could eliminate the ability of an antibody to recognize this altered antigen. If the range of decreased binding ability after single

point mutation of a protein antigen varies, one could expect point mutations in the protein antigen to cause varying degrees of loss of protection, depending on the relative importance to the binding interaction of the altered residue. Alternatively, the combined effects of multiple changes in an antigenic determinant could again result in loss of protection. A protein having multiple antigenic sites, multiple point mutations, or accumulated point mutations at key residues could create a new antigen that is precipitously or progressively unrecognizable by any of the antibodies in the polyclonal pool. Thus, proteins of different levels of homology may not induce antibody which is recognized by the "native" protein on the *S.pneumoniae* bacteria, and be ineffective in "treating" infections caused by *S.pneumoniae*.

The specification has not enabled the full-length protein, let alone fragments or homologous proteins, for use as a vaccine. There are no results provided from active immunizations, let alone challenge experiments which would demonstrate the vaccine's ability to protect against disease. The specification provides teaches how to make hyperimmune serum through injection of the full-length protein set forth in SEQ ID NO:2. In vitro assays which demonstrate the serum's opsonophagocytic activity are provided. However, no experiments, results or methods are described which demonstrate full-length protein, let alone fragments or homologous proteins, ability to act as a vaccine. There are no results from active immunization experiments. Additionally, if additional evidences are provided by Applicants experiments using the full-length protein will not enable fragments. The specification fails to teach the location, if any, of immunoprotective epitopes. Often times it takes more than one epitope to provide

immune protection. With respect to homologous or equivalent sequences, as stated above, no guidance as to what amino acids may be changed without causing a detrimental effect to the protein to be produced is provided.

When considering a bacterial antigen as a vaccine candidate, three major considerations must be raised (1) the antigen must be conserved among strains of the bacterial species whose disease one wishes to prevent; (2) it must generate protective antibody such that the antibody to the antigen prevents disease; and (3) it must be a good immunogen such that protective antibodies are elicited in the population at risk and that these antibodies persist for sufficient time to provide protection throughout the risk period. Even when an antigen meets these three considerations, further testing often indicates that the antigen will not be effective as a vaccine. The instant specification fails to demonstrate that PMP meets any of the three considerations known in the art to be important when considering a bacterial antigen as a vaccine candidate. Without specific guidance from the specification, it would take undue experimentation for those skilled in the art to make and/or use the claimed invention. Applicants should provide additional evidence, such as challenge experiments, to demonstrate PMP's ability as a vaccine, or they may show less extenisve studies to enable "treatment" methods (for example, some therapeutic benefit or reduction in symptoms) *or* they should amend the claims to 'methods of raising an immune response' (using the full-length protein) in order to overcome this rejection.

Lastly, some of the claims are drawn to fragments or equivalent sequences which maintain function, i.e., protease maturation function. However, the specification has assigned

the Pmp function based solely on sequence homology analysis. It has not been shown that the claimed protein definitively possesses this function. Accordingly, it is even more unclear which fragments of the claimed protein would be necessary to maintain this function.

The scope of the instant claims is not enabled by the instant specification. Given the lack of guidance contained in the specification and the unpredictability for determining acceptable amino acid substitutions, one of skill in the art could not make or use the broadly claimed invention without undue experimentation.

Claim Rejections - 35 USC § 102

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371© of this title before the invention thereof by the applicant for patent.

8. Claims 20-27, 30-33 and 36-38 are rejected under 35 U.S.C. 102(b) as being anticipated by Kunsch et al (WO 98/18930).

Kunsch et al teach antigens and vaccines to prevent or attenuate infections caused by bacteria of the *Streptococcus* genus and *S.pneumoniae* in particular. See abstract and page 115. The vaccine encompasses a polypeptide or fragment thereof contained in Table 1. Table 1 discloses a polypeptide which has 213 identical amino acids to Applicants' SEQ ID NO:2.

See attached sequence alignment. The instant claims encompass fragments and use the open language "comprising". Accordingly, the polypeptide and/or its fragments to be used in the vaccines read on the instant claims. The reference teaches that the vaccine may be prepared with a carrier and/or an adjuvant and is suitable to elicit protective antibodies in the vaccinated animal. See pages 4-5. Although the reference does not use the name "protease maturation protein" to describe their protein, the structure is the same and therefore the protein would inherently possess this function. Recombinant methods of producing the protein and/or epitope-bearing portions are also taught. See page 3, line 32- page 33, line 5.

9. Claims 20-27, 30-33 and 36-38 are rejected under 35 U.S.C. 102(e) as being anticipated by Black et al (US 6,348,328 B1).

Black et al teach a polypeptide which has 48 identical amino acids to Applicants' SEQ ID NO:2 and a 97% local similarity. See attached sequence alignment. Black et al teach that the polypeptide is from *S.pneumoniae*. It is taught that the proteins or their fragments may be used in pharmaceutical compositions or vaccines along with a carrier and or an adjuvant to treat infections caused by the bacteria. The manufacture of such medicaments is also taught. See columns 16-17. See column 20, lines 33-41 for vaccine teachings. Recombinant production of the polypeptides is also taught. Although the reference does not use the name "protease maturation protein" to describe their protein, the structure is the same and therefore the protein would inherently possess this function.

12. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal

Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15,1989). The Group 1641 Fax number is (703) 872-9306 which is able to receive transmissions 24 hours/day, 7 days/week.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer E. Graser whose telephone number is (703) 872-9306. The examiner can normally be reached on Monday-Friday from 7:00 AM-4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith, can be reached on (703) 308-3909.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.